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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,033	05/11/2001	Pierre Chambon	065691-0222	5081

22428 7590 06/25/2003

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,033	CHAMBON ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *9,13,15-18,21,22,24-32,35-49,51 and 53-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-12,14,19,20,23,33,34,50 and 52* is/are rejected.

7)☒ Claim(s) *2,4,5 and 9-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-61 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group ix in Paper No. 12 is acknowledged. Applicants further elected Cre recombinase from claim 2, LoxP from claim 4, all or part of D hinge region of a nuclear estrogen receptor from claim 5, and RXRα from claim 19. Applicants traverse the restriction requirement on the ground(s) that search of groups i-xii would not be a serious burden because transgenic metazoan organism all comprises a Cre-ER gene under the control of different expression element. Further, Applicants traverse the election of one element from claims 2, 4, 5, and 19 because Applicants consider there is sufficiently few numbers of members within the Markush group. This is not found persuasive because the inventions of Groups i-xii are patentably distinct for reasons set forth of the record mailed on 2/31/03. Although all transgenic metazoan organisms comprise a Cre-ER gene, the DNA encoding said gene is different. In addition, the controlling element is different in each group. A search of one group is not co-extensive with the each of another; therefore, a search of all 12 groups is burdensome. In addition, a transgenic metazoan organism comprising one member from 2, 4, 5 and 19 would result in different genetic makeup from a transgenic metazoan organism comprising another member from these claims. Therefore, the invention is patentably distinct from each other. Applicants are reminded that this election is a restriction requirement rather than a species election.

The restriction requirement is still deemed proper and is therefore made FINAL. Accordingly, claims 9, 13, 15-18, 21, 22, 24-32, 35-49, 51, 53-61 are withdrawn from

consideration for being directed to non-elected subject matter. Claims 1-8, 10-12, 14, 19, 20, 23, 33, 34, 50 and 52 are currently under examination.

Drawings

The drawings are objected to because of the informalities as indicated by Draftsperson on PTO form 948 (see attached form). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. Any response to this office action which does not respond to the above objections will be considered non-responsive.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 10/3/2000. It is noted, however, that applicant has not filed a certified copy of the French application as required by 35 U.S.C. 119(b).

Claim Objections

Claims 2, 4, 5, 19 and 52 are objected to for containing non-elected subject matter. Amending the claims such that they are only directed to elected inventions is required.

Claim 10 is objected to as being dependent upon a non-elected claim (25). Applicant is advised to rewrite the claim in independent form including all of the limitations of the base claim (25).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-12, 14, 19, 20, 23, 33 and 34 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims encompass any type of metazoan organism comprising in at least one cell 1) a fusion protein comprising a recombinase, a hinge region, and a polypeptide comprising the ligand binding domain of the human nuclear

estrogen receptor; 2) one or more gene of interest flanked by recognition sites of said recombinase, which is a vast genus of organisms. The specification only describes a transgenic mouse comprising claimed elements. The specification fails to describe any other transgenic or non transgenic metazoan organism comprising claimed elements. As such, the specification fails to describe a representative number of species by their complete structure or other identifying characteristics. Therefore, the written description requirement is not met.

The claims also recite natural variants or fragments of human or vertebrate nuclear estrogen receptor (claims 1 and 7). However, the specification only discloses a fusion protein comprising Cre and ligand binding domain of human nuclear estrogen receptor. The specification fails to describe any other fragments or variants of said ER that retains the function of inducing Cre recombinase activity upon synthetic ligand binding. As such, the structural functional relationship is missing. Therefore, the written description requirement is not met.

The claims also encompass a natural or synthetic variant of the claimed recombinase (claims 2 and 3). The specification fails to disclose any natural or synthetic variant of recombinase that retains the function in the transgenic system. The specification also fails to disclose the size and which part of the claimed recombinases is required for their function. As such, the structural and functional relationship is missing. Therefore, the specification fails to describe the invention in such a way to convey one skilled in the art that the inventors had possession of the entire genus of the claimed invention at the time the application was filed.

Claims 1-8, 10-12, 14, 19, 20, 23, 33, 34 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result

in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits transgene dependent phenotype, does not reasonably provide enablement for any metazoan organism comprising a cell comprising claimed transgenes. Further, the specification does not enable any metazoan organism without any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Nature of the invention:

The nature of the invention is a metazoan organism comprising in at least one of the cells a) a first expression cassette encoding a fusion of a recombinase and human estrogen receptor (ER) linked by a hinge region; b) a endogenous gene of interest flanked by one or more recognition sites of the recombinase; wherein the recombinase has no activity when natural ligand of the ER is administered, but activated when a synthetic ligand having antagonistic activity is administered.

Breadth of the claim:

The breadth of the claim encompasses any type of metazoan organism, either transgenic or non transgenic, that comprises claimed expression cassette in any types of cell. The specification does not provide an enabling disclosure for the full scope of the metazoan organism as claimed. The only embodiment enabled by the specification within the scope of the claims is a transgenic mouse comprising a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment

but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits transgene dependent phenotype. Thus the breadth of the claims is very broad that surpasses enabling disclosure of specification.

Amount of guidance in the specification and Working Examples:

The specification discloses a transgenic mouse comprising an expression cassette comprising a Cre recombinase fused to a modified ER under the control of aP2 promoter, wherein said modification results in conditional activation of Cre upon ligand binding to ER; and endogenous RXRα disrupted by replacing a portion of the endogenous gene with tkneo selection marker flanked by two lox P sites; wherein administering tamoxifen to said mouse results in activation of Cre recombinase specifically in adipose tissue, wherein such activation results in excision of the tkneo gene, and said mouse exhibits the phenotype of altered lipid metabolism. The specification and the working examples provide sufficient guidance to use the invention as diabetic disease model. However, the specification does not teach how to make other types of metazoan organism that has the claimed genotype and with same phenotype. The specification also fails to teach how to use metazoan organism that has the claimed genotype but without any phenotype.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the

working examples provide sufficient guidance to practice the invention with only a transgenic mouse comprising an expression cassette comprising a Cre recombinase fused to a modified ER under the control of aP2 promoter, wherein said modification results in conditional activation of Cre upon ligand binding to ER; and endogenous RXRα disrupted by replacing a portion of the endogenous gene with tkneo selection marker flanked by two lox P sites; wherein administering tamoxifen to said mouse results in activation of Cre recombinase specifically in adipose tissue, wherein such activation results in excision of the tkneo gene, and said mouse exhibits the phenotype of altered lipid metabolism. However, neither the specification nor the working examples provide enough guidance on how to make and use the invention with any and all metazoan organism carrying the transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification only discloses the phenotype of a transgenic mouse with selective RXRα deletion in adipose tissue but fails to disclose the phenotypes of any and all metazoan organism with a disruption in the any gene and in any tissue. Given the state of the art, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals and/or other metazoan organism, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the disclosure, while being enabling for a transgenic mouse comprising a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits transgene dependent phenotype, does not provide sufficient support to predict the same phenotype in other metazoan organism systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not predictable. For example, Jacks et al. (1992) describe Rb knockout mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the phenotype of transgenic or non transgenic metazoan organism with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of metazoan organisms besides transgenic mice having selective gene deletion in specific

tissue upon ligand induction, because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of metazoan having the selective gene disruption. According to the disclosure, the claimed transgenic mouse is generated by crossing a first transgenic mouse comprising Cre-ER under the control of a tissue specific promoter and a second transgenic mouse having loxP recombinant sites and/or selection markers inserted into the region that flanks the gene of interest that is to be deleted. The insertion of recombinant sites and selection markers can only be accomplished by homologous recombination in mouse ES cells. Therefore, embryonic stem (ES) cell technology must be available to carry out the method. The prior art does not teach the generation of a transgenic mouse from any other types of cells. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1). Thus, metazoan organism with targeted deletion of an endogenous gene cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of

using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed metazoan organism other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic mice with a tissue specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a transgenic mouse comprising a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene results in a transgene dependent phenotype

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 5, 20 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 2 and 3, the recitation of "of the bacterial β recombinase" on line 10 renders the claim indefinite because it is unclear what subject matter Applicants are claiming. It appears that a word is missing before this phrase. Appropriate correction is required.

Claims 4 and 5 recites the limitation "said Cre recombinase" in line 2. There is insufficient antecedent basis for this limitation in the claim. The parent claim, claim 1, does not have this limitation.

Regarding claims 20 and 34, the phrase "in particular" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 8, 10-12, 14, 20, 33 and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Indra et al.

Indra et al. disclose that transgenic mice comprising Cre-ER^{T2} under the control of K5 promoter are crossed with reporter mice which comprises loxP-CAT-loxP-lacZ cassette, and subsequently mice with both transgene cassette are generated (see page 4326, col.1). Indra et al. further disclose that oral or topical tamoxifen administeration results selective deletion of the CAT gene and results in β-gal staining in mouse keratinocytes (see page 4326, col.1). Therefore, Indra et al. disclose the instantly claimed invention.

Claims 1-5, 7, 8, 10-11, 19, 20, 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Feil et al.

Feil et al. disclose the generation of a double transgenic mouse comprising a reporter cassette that comprises tkneo selection marker flanked by two lox P sites that integrated into RXRα allele, and another cassette comprising Cre-ER^T under the control of CMV promoter (see page 10888, 2nd col., 2-4 paragraph). Feil et al. further disclose OHT administration resulted Cre-mediated excision of RXRα gene (see page 10888, 2nd col., 4th paragraph). Therefore, Feil et al. disclose the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Indra et al. and Feil et al., in view of Ross et al. and Tontonoz et al. (1997, PNAS, Vol.94, pp.237-241)

The teachings of Indra et al. and Feil et al. are discussed above. However, neither Indra et al. and Feil et al. teaches a transgenic mouse comprising tkneo selection marker flanked by two lox P sites that integrated into RXRα allele, and another cassette comprising Cre-ER^T under the control of aP2 promoter.

Ross et al. teach an adipocyte specific promoter aP2 that confer adipocyte specific expression in transgenic mouse (see abstract and Table 1). Ross et al. further teach a 5.4 kb 5' flanking region of aP2 gene confers the highest promoter activity (see Figure 1B).

Tontonoz et al. teach peroxisome proliferator-activated receptor and RXRα form a heterodimeric complex that functions as a central regulator of adipocyte differentiation (see page 237, 2nd col., 2nd paragraph). Tontonoz et al. also teach that activators of RXRα may be useful in treating liposarcoma in humans because the regulatory role of RXRα plays in adipocyte differentiation.

It would have been obvious to one of ordinary skill of art to make a transgenic mouse with selective RXRα disruption in adipose tissue based on the combined teaching of Indra et al. and Feil et al., Ross et al. and Tontonoz et al. The ordinary skilled artisan would have been motivated to do so to study the precise function of RXRα because the implication of RXRα's role in regulating adipocyte differentiation and possible role as a target for pharmacological intervention of liposarcoma in humans. Based on the teaching of Indra et al and Feil et al., one of ordinary skill of art would make a such a transgenic mouse by crossing the transgenic mouse comprising a Cre-ER fusion protein under control of aP2 promoter (as taught by Ross et al.) and

a second transgenic mouse comprising modified RXRα allele comprising lox P sites to generate a double transgenic mouse, and subsequently treating the offspring with tamoxifen to induce tissue specific Cre expression and result in excision of the RXRα target gene. The level of skill in the art is high. Absent evidence to the contrary, one ordinary skill of art would have reasonable expectation of success to make such double transgenic mouse. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al., in view of Schwenk et al.

The teaching of Feil et al. is discussed above. However, Feil et al. do not teach a transgenic mouse comprising a transgene comprising a D hinge region of SEQ ID NO:2 from 282-301.

Schwenk et al. teach the generation of a fusion construct comprising Cre and a VRGS linker and ligand binding domain of ER starting from amino acid 304 (see page 1427, 2nd col., 4th paragraph). Schwenk et al. teach that such construct is ligand inducible and capable of generate B cell specific gene deletion in mice (see page 1430, 3rd paragraph).

It would have been obvious to one of ordinary skill of art to use any linker for attachment of ER ligand binding domain to Cre recombinase based on the teaching of Feil et al. and Schwenk et al. because the linker does not affect the conditional induction of Cre recombinase. One of ordinary skill in the art would have been motivated to use D hinge region of SEQ ID NO:2 from 282-301 as linker to fuse the Cre and human ER because it is native to the human ER and ease of manipulation. The level of skill in the art of molecular cloning is high. Absent

evidence to the contrary, one of ordinary skill of art would have reasonable expectation of success to fuse human ER with D hinge region from 282-301 with Cre recombinase. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 13, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER